REMARKS

Claims 1-8 and 11-16 were pending. Claims 1-5 and 14 are currently amended. No new matter has been added. Support for the amendments to the claims can be found throughout the specification and claims as filed and in particular paragraphs [0051]-[0069] and the Examples. In view of the arguments provided herein, Applicants respectfully request reconsideration of claims 1-8 and 11-16.

In accordance with the Exminer's request, Applicants have submitted clean copies of the figures with this response, noted as Replacement Sheets, to address the Examiner's concerns with the "grey" vs "black" plots in the figures.

Rejections under 35 USC § 112, second paragraph

Applicants traverse the rejections over claims 1-8 and 11-16 under 35 U.S.C. § 112, second paragraph, as being indefinite allegedly for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant contends that the rejections with respect to claims 1-8 and 11-16 are moot in view of Applicant's amendments to the claims.

Specifically, claim 1 has been amended to coordinate the preamble of "characterizing" with the final method step of "characterizing". Further, Applicant has clarified the final "wherein" clause to address the Examiner's concerns. Accordingly, Applicant respectfully requests withdrawal of the Examiner's rejections under 35 U.S.C. § 112.

Rejections under 35 USC § 112, first paragraph

The Examiner has rejected claims 1-8 and 11-16 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

First, Applicants have amended claim 1 to recite "human subject" to address the Examiner's concern that the claims encompass determination in human and non-human subjects.

Applicants submit that the amendment to claim 1 reciting that the sample is "from a biological fluid containing DNA from breast cells or tissue; breast tissue; or breast cell sample from the subject having or at risk of having a cell proliferative disorder of the breast" obviates the Examiner's concerns regarding the list of samples provided in claim 11. In nearly all cancers, cells slough off from the primary tumor or site and enter the bloodstream or other biological systems, therefore as long as the sample being analyzed contains breast tissue or cells from the breast, Applicants submit that the claims are fully enabled. Support for the amendment can be found for example in paragraph [0069] where biological samples are described as: "cell lines, histological slides, paraffin embedded tissues, biopsies, tissue embedded in paraffin, bodily fluids, urine, blood and all possible combinations thereof. In a particularly preferred embodiment of the method said source is bodily fluids urine, or blood." In addition, the reference described below as Exhibit E provides further support for the amendments to claim 1 with respect to the biological sample, and in particular the use of biological/bodily fluids as disclosed by Applicants in paragraph [0069].

Applicant maintains that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir., 1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." In re Anderson, 471 F.2d 1237, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. In re Anderson, at 1241 (citing Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 [1935]). Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every

such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 499, 502 (CCPA 1960). There is, therefore, no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed.

Applicant has provided an enabling disclosure for determination of PITX2 as an important prognostic marker of breast cancer and described in detail how PITX2 is used for analysis of methylation status and correlation with disease (e.g., disease-free survival; propensity for metastases). Now that Applicant has provided such information, the claims are specifically directed to the use of PITX2 for such purposes which are encompassed in the claimed phrase "characterizing".

Example 1 of the specification provides an outline of the data analyses methods (e.g., beginning at [0375]-[0401]; determination of disease-free survival ([0385]-[0388]; [0401]); analysis of methylation patterns for determination of therapeutic responsiveness (e.g., Tamoxifen) ([0389]-[0394] (Figures 41; 52-54 (see [0314]; Figures 61-62 [0321]-[0322]; Figures 71-71 [0331]-[0332]) and likelihood of distant relapse/metastases ([[0051]-[0066]; Figures 35-46). In order to advance prosecution, Applicants have amended claim 1 to more particularly define "characterizing" as including the prognosis of said subject disease free survival or likelihood of metastases of said subject; and/or probability of response of said subject to one or more treatment regimens. Applicants submit that Example 1, the figures identified above, and the specification as filed provide enablement for the use of the PITX2 gene methylation status for determining prognosis, distant relapse (metastases) vs. metastases free survival; and/or disease-free survival and/or probability of response to a treatment regimen (e.g., Tamoxifen), in contrast to the Examiner's assertions that no working examples are provided for PITX2.

Further, Applicants point to Example 2 of the application, beginning at [0402], where PITX2 (SEQ ID NO:23) in addition to other genes were validated as being effective markers for

characterizing breast cancer. Paragraphs [0471]-[0480] provide data on two clinical endpoints used: disease-free survival and metastasis-free survival. Figures 61, 62, 103, 71, 72, 73 and 74 in particular provide clear data regarding the results of the assays showing that PITX2 is a marker capable of providing characterization of breast cancer as described above.

In addition, post-filing evidence further supports Applicants data and enabling disclosure. Exhibit A shows that PITX2 DNA methylation was used as a marker for outcome prediction in Tamoxifen-treated, node-negative breast cancer patients. The tests allowed a prediction of low-risk patients for example, who may be treated by tamoxifen alone.

Exhibit B shows that DNA methylation of PITX2 predicts the risk of distant disease recurrence (metastases) in breast cancer patients.

Exhibit C provides support that PITX2 DNA methylation is a marker for disease recurrence and progression in lymph node-negative (LNN), steroid hormone receptor-positive breast cancer patients.

Exhibit D shows that PITX2 DNA methylation predicts outcomes with respect to risk of distant recurrence in certain breast cancer patients.

Exhibit E shows that PITX2 DNA methylation in samples of blood and bone marrow plasma of breast cancer patients correlated with overall survival and distant disease free survival.

Exhibit F shows that PITX2 DNA methylation is a marker for assessment of prognosis or prediction of a therapeutic response in patients with breast cancer. The marker was also used to show outcome predictions in early breast cancer patients treated with tamoxifen therapy.

With respect to predictability, the Examiner notes that the claims do not require a comparison step with a control. Applicants note that claim 1 has been amended to recite such a step, in particular, "wherein an increased methylation status in the sample as compared with methylation status in a control sample from a subject not having or at risk of having a cell proliferative disorder of the breast tissue, provides characterization of the cell proliferative disorder." Accordingly, Applicants submit that the comparison step adds the control for methylation status and adds certainty to the detection method.

Applicants submit that the claims as amended are fully enabled by the specification as filed and further supported by numerous post-filing references. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §112.

CONCLUSION

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Applicant believes that no fee is deemed necessary with the filing of this paper. However, the Commissioner is authorized to charge any fees deemed necessary with the filing of this paper, or credit any overpayments, to Deposit Account No. 07-1896 referencing the above-identified docket number.

Respectfully submitted,

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